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Breast Cancer Mortality After Diagnostic Radiography

Findings From the U.S. Scoliosis Cohort Study

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Study Design. A retrospective cohort study was conducted in 5573 female patients with scoliosis who were referred for treatment at 14 orthopedic medical centers in the United States. Patients were less than 20 years of age at diagnosis which occurred between 1912 and 1965.

Objectives. To evaluate patterns in breast cancer mortality among women with scoliosis, with special emphasis on risk associated with diagnostic radiograph exposures.

Summary of Background Data. A pilot study of 1030 women with scoliosis revealed a nearly twofold statistically significant increased risk for incident breast cancer. Although based on only 11 cases, findings were consistent with radiation as a causative factor.

Methods. Medical records were reviewed for information on personal characteristics and scoliosis history. Diagnostic radiograph exposures were tabulated based on review of radiographs, radiology reports in the medical records, radiograph jackets, and radiology log books. Radiation doses were estimated for individual examinations. The mortality rate of the cohort through January 1, 1997, was determined by using state and national vital statistics records and was compared with that of women in the general U. S. population.

Results. Nearly 138,000 radiographic examinations were recorded. The average number of examinations per patient was 24.7 (range, 0–618); mean estimated cumulative radiation dose to the breast was 10.8 cGy (range, 0–170). After excluding patients with missing information, 5466 patients were included in breast cancer mortality analyses. Their mean age at diagnosis was 10.6 years and average length of follow-up was 40.1 years. There were 77 breast cancer deaths observed compared with the 45.6 deaths expected on the basis of U.S. mortality rates (standardized mortality ratio [SMR] = 1.69; 95% confidence interval [CI] = 1.3–2.1). Risk increased significantly with increasing number of radiograph exposures and with cumulative radiation dose. The unadjusted excess relative risk per Gy was 5.4 (95% CI = 1.2–14.1); when analyses were restricted to patients who had undergone at least one radiographic examination, the risk estimate was 2.7 (95% CI = −0.2–9.3).

Conclusions. These data suggest that exposure to multiple diagnostic radiographic examinations during childhood and adolescence may increase the risk of breast cancer among women with scoliosis; however, potential confounding between radiation dose and severity of disease and thus with reproductive history may explain some of the increased risk observed. [Key words: breast neoplasms, radiation-induced, cohort study, epidemiology, mortality, radiation, radiography, scoliosis] **Spine 2000;25:2052–2063**

Studies of the atomic bomb survivors,[28] patients with tuberculosis who underwent multiple fluoroscopic examinations during treatment,[3,14,23] and patients who underwent therapeutic irradiation for a variety of conditions, including benign breast disease,[22] acute postpartum mastitis,[32] enlarged thymus,[12] Hodgkin's disease,[2] and skin hemangiomas,[21] have established that exposure to ionizing radiation increases the risk of breast cancer. Age at exposure has been found to modify response to radiation, with childhood exposures conferring the highest risk and exposure after age 40 imparting low or minimal risk.[4,18] It has been hypothesized that the period between Tanner stage breast-2[33] and the onset of menarche may be a particularly sensitive biologic stage with respect to the action of radiation and other environmental carcinogens.[15] No such pattern has been apparent among atomic bomb survivors and other populations exposed during childhood and adolescence,[17,34,35] but published analyses have not focused on the narrow range of exposure ages relevant to the hypothesis.

Study of women with scoliosis may provide additional insight into the risk of breast cancer after low-dose radiation exposures received during childhood and adolescence. Depending on the magnitude of the spinal curvature, patients typically undergo routine diagnostic radiographic examinations of the spine throughout the growth spurt to monitor for curve progression. An initial pilot study of 1030 women, diagnosed in any of three hospitals or one clinic in Minneapolis–St. Paul, Minnesota, identified a nearly twofold risk of incident breast cancer that was consistent with a radiation effect.[13] The number of breast cancer cases was small (n = 11), however, and did not allow for adjustment for possible con-

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Table 1. Vital Status of Scoliosis Patients as of January 1, 1997 by Medical Center

Medical Center	No. of Patients	Calendar Year of Diagnosis	Lost to Follow-Up <1979 No.	Lost to Follow-Up <1979 Percent	Lost to Follow-Up 1979+ No.	Lost to Follow-Up 1979+ Percent	Deceased No.	Deceased Percent	Alive No.	Alive Percent	Average Follow-Up (yr)*
Total	5573	1912–65	474	8.5	128	2.3	1046	18.8	3925	70.4	40.5
Pilot Study Centers† (Minneapolis-St. Paul, MN)	1025	1922–65	7	0.7	17	1.7	97	9.5	904	88.2	37.2
Alfred I. DuPont Institute (Wilmington, DE)	403	1939–65	22	5.5	7	1.7	28	7.0	346	85.9	34.8
Children's Hospital (Boston, MA)	1436	1916–65	170	11.8	40	2.8	274	19.1	952	66.3	45.4
Shriner's Hospital for Crippled Children (Chicago, IL)	296	1913–65	27	9.1	10	3.4	71	24.0	188	63.5	38.4
Shriner's Hospital for Crippled Children (Greenville, SC)	245	1918–65	25	10.2	5	2.0	56	22.9	159	64.9	37.1
Shriner's Hospital for Crippled Children (Philadelphia, PA)	267	1925–65	24	9.0	6	2.3	70	26.2	167	62.6	39.7
Shriner's Hospital for Crippled Children (Portland, OR)	280	1913–65	31	11.1	3	1.1	70	25.0	176	62.9	41.6
Shriner's Hospital for Crippled Children (San Francisco, CA)	301	1912–65	54	17.9	11	3.7	62	20.6	174	57.8	39.0
Shriner's Hospital for Crippled Children (Springfield, MA)	377	1915–65	46	12.2	4	1.1	82	21.8	245	65.0	41.8
Shriner's Hospital for Crippled Children (St. Louis, MO)	481	1914–65	48	10.0	10	2.1	141	29.3	282	58.6	38.9
University Hospital Rehabilitation Center (Hershey, PA)	437	1924–65	19	4.4	12	2.8	88	20.1	318	72.8	41.5
Multiple Centers	25	1927–65	1	4.0	3	12.0	7	28.0	14	56.0	40.1

* Excluding 18 patients with missing dates of vital status.
† Includes Twin Cities Spine Center, University of Minnesota Hospital, Gillette Children's Hospital, and Fairview-St. Mary's Hospital.

founders, factors that might be related both to scoliosis and breast cancer risk, such as reproductive history.

The pilot study was expanded to improve statistical power and obtain information from living subjects on potential confounding factors. Approximately 4500 female patients were enrolled from 10 of the largest orthopedic medical centers in the United States. The current article presents findings from an evaluation of breast cancer mortality after diagnostic radiograph exposures.

Materials and Methods

Study Population. The study population consisted of 5573 women with confirmed diagnoses of scoliosis, kyphosis, lordosis, or kyphoscoliosis (hereafter referred to as scoliosis) who were seen during childhood or adolescence at any of 14 large orthopedic medical centers in the United States (see Table 1). Patients with congenital scoliosis were included in the pilot study (n = 161) but, because of the likelihood of other serious medical conditions for which they may have received a substantial number of radiographic examinations elsewhere, no additional congenital cases were enrolled. Patients were excluded from study if they were male (n = 576), had scoliosis diagnosed after 1965 (n = 69), were more than 19 years of age at diagnosis (n = 4), had a history of cancer or radiotherapy (n = 28), or satisfied other exclusion criteria (n = 352), including congenital origin and other characteristics that could have been associated with multiple radiograph exposures at other nonparticipating institutions.

Medical Records and Radiographic Examinations. Data on personal characteristics and on diagnosis and treatment of scoliosis were abstracted from medical records. Radiology reports, radiographs, radiograph jackets, and radiology log books were reviewed, and the following information was recorded for individual radiographic examinations: date, field (*e.g.*, full spine, thoracolumbar spine), view (*e.g.*, anteroposterior, posteroanterior, lateral), position (*e.g.*, standing, supine), presence of an orthosis (cast, brace, or surgical implant), radiograph size, whether the breast was in the radiograph beam, and radiograph machine parameters. There were 32,807 radiographic examinations (23.8%) for which it was not possible to differentiate between the anteroposterior and posteroanterior view. A careful review of the data for the other films from each medical center suggested that, except in one center, the anteroposterior view was used almost exclusively throughout the study period. At the Dupont Institute (Wilmington, DE), there was a clear shift to the use of posteroanterior views beginning in 1981.

For examination information derived from radiographs, the breast was considered to be definitely in the radiation beam if three or more ribs were included or if the radiograph size was 14 × 36 in., and probably in the beam if two or more ribs were included. A review of radiographs in which the matching radiology report specified a field of cervical spine, lumbar spine, or abdomen showed that the breast was exposed to the beam in 75%, 71%, and 75% of these examinations, respectively. Thus, for examinations derived from radiology reports, the breast was considered to have definite exposure for fields of full spine, cervicothoracic spine, thoracic spine, thoracolumbar spine, upper spine, upper and lower spine, and chest and probable exposure for fields of cervical spine, lumbar spine, and abdomen. There were 35,653 examinations (25.9%) for which

Table 2. Estimated Radiation Dose to Breast (cGy) From a Full Spine Radiographic Examination, by Age at Exam and Calendar Time Period

Age at Radiographic Exam, Yr/View	1940–59	1960–75	1976–89
≥13			
AP	0.588	0.350	0.090
PA	0.005	0.005	0.005
LAT	0.300	0.225	*
<13			
AP	0.780	0.470	0.125
PA	0.003	0.003	0.003
LAT	0.300	0.225	*

* Parameters were not available for this view in this time period.

the probable presence of the breast in beam was logically determined based on field or radiograph size.

Dosimetry. Dose to the breast was estimated for each examination in which the breast was in the radiation beam; examinations in which the breast was not exposed to the beam were assumed to contribute no dose. For each radiographic examination, a patient was classified as preteen (<13) or teen or adult (≥13) according to her age at the time. The breast dose was estimated for preteens at a depth of 1.0 cm and for adults at 2.5 cm. Doses for each examination were calculated by computer (XRayDose software package; MHP Software, N. Little Rock, AR) based on organ doses calculated by Rosenstein.[30] Because radiology techniques have changed dramatically since 1920, breast doses for each type of examination were estimated separately for the following periods: 1920–1939, 1940–1959, 1960–1975, and 1976–1989.

Despite intensive efforts, none of the actual radiograph machines could be located for measurement studies. Information was available, however, on the manufacturers and models for machines used in the pilot study centers, and all 10 of the expanded study institutions completed a standardized questionnaire concerning the machines and parameters in use during the study period. The manufacturers and models for the machines used in the 14 participating institutions were similar.

Machine parameters for diagnostic radiographic examinations are rarely recorded in patient charts, because they are remarkably uniform for any given generation of radiograph machine. That is, there is one set of parameters that normally provides the optimal picture, with some variation to allow for the thickness of the patient. Five medical centers provided patient radiograph examination records containing specific parameter information for 290 patients, of which 276 were from one institution (University Hospital Rehabilitation Center, Hershey, PA). The Hershey data were used to select one set of parameters per view for the entire population for a given period. Machine parameters were available for 4,791 of 12,019 (40%) documented examinations among the 276 patients. Each patient record was abstracted for radiograph view, patient diameter, peak kilovoltage, milliampere-seconds, and source–image distance for examinations that included the breast. The machine parameters from the hospital questionnaires were compared with the individual patient parameters from Hershey, and the agreement was excellent. Most examinations were spinal radiographic examinations. Table 2 shows the estimated breast doses from different views for three periods: 1940–1959, 1960–1975, and 1976–1989.

No parameters were available for any hospital in 1920 to 1939. Because it is likely that patients received high exposures during this period, the doses for 1920–1939 were estimated by doubling the dose calculated for 1940–1959, according to the recommendation of an expert on diagnostic physics (Dr. Louis K. Wagner, University of Texas Medical School, Houston, TX, personal communication, 1997). Only 6% of the examinations occurred before 1940; thus, uncertainties in these doses would have limited impact on the findings. For the small number of fluoroscopy examinations (n = 264), the dose was estimated to be twice that for conventional full-spine radiographic examinations during the same period. The medical indication for these examinations is unknown, although it is unlikely that fluoroscopy was used to image the spine.

Information was not sufficient to estimate doses for 18,583 (13.5%) documented radiographic examinations. Of these, 16,422 (88.4%) were assigned the mean dose for all other examinations received by the same patient, and 2,160 (11.6%) were assigned the mean dose for examinations received by other patients who were similar in age, calendar year, and medical center. One patient who was 36.5 years or age at the time of examination could not be matched, and no dose was estimated. Among all patients, the average estimated cumulative dose to the breast was 10.8 cGy (range, 0–170).

Follow-up. Patient follow-up was complicated by the fact that most patients were last seen as teenagers, and information was not generally available on name changes in later marriages. Therefore, telephone tracers conducted one-on-one tracing of fathers, mothers, and husbands (on identification), in addition to patients. Social security numbers were determined for 5264 patients (94.5%). Tracing resources included records from the Social Security Administration, Health Care Financing Administration, National Death Index, town books (in Massachusetts), motor vehicle bureaus, credit companies, the U.S. Postal Service, telephone directory assistance, commercial telephone listings, and neighbor search databases. Death certificates were obtained for decedents from state vital statistics offices, and causes of death were coded by trained nosologists according to the World Health Organization.[37]

Statistical Procedures. Vital status was determined through January 1, 1997 (Table 1). Accrual of woman-years at risk began at the date of scoliosis diagnosis for patients from the 10 expanded study centers and at diagnosis plus 3 years for pilot study subjects (eligibility for the pilot study included a minimum 3-year survival period). Follow-up ended at the date of death, date last known to be alive for patients who were lost to follow-up, or January 1, 1997. Excluded from the overall mortality analysis were 34 patients who contributed no woman-years of follow-up and 18 for whom exit dates were missing. An additional 55 women who were known to have died but for whom cause of death was unknown were excluded from the breast cancer analyses.

The mortality rate of patients with scoliosis was compared with that of white females in the United States. Numbers of expected deaths, by cause, were calculated by multiplying the age- and calendar-specific woman-years at risk, in 5-year intervals, by the corresponding mortality rates in the general population.[24] Standardized mortality ratios (SMRs) were computed by dividing the number of observed deaths by the number of deaths expected. An SMR of 1.00 indicated that patients with scoliosis had the same death rate as the general population, whereas an SMR of 1.70 indicated a 70% higher rate. Internal cohort comparisons were based on relative risks (RRs) obtained by dividing the individual SMRs by the SMR for a reference group.

Exact and asymptotic methods were used to calculate 95% confidence limits (CI) and statistical significance levels for SMRs, relative risks, and tests for nonhomogeneity and trend among different levels of a factor.[6,7] Cochran's theorem[8] was used to partition χ^2 into independent components corresponding to trend with dose and residuals. Linear model excess relative risk (ERR) per unit dose of radiation was modeled using the computer for regression analysis (Amfit program for Poisson regression; Hirosoft International Corp., Seattle WA).[29] In that analysis, it was assumed that observed numbers of breast cancer deaths in different groups defined by birth year, calendar time, and other factors, corresponded to independent Poisson variables Y, with means

$$E(Y) = \mu \times (1 + \alpha D) \times \exp(\beta_1 x_1 + \ldots + \beta_k x_k),$$

where μ is the expected frequency based on relevant, age-specific population rates; α, $\beta_1, \ldots, \beta_k$ are unknown parameters that can be estimated from the data; D is radiation dose; and $x_1, \ldots, x_k$ are various risk factors of interest, other than radiation dose. Risk for exposures accrued during potentially radiosensitive age intervals were similarly evaluated, replacing αD by $\alpha_1 D_1 + \ldots + \alpha_4 D_4$, where the subscripts correspond to four different age-at-exposure intervals.

■ Results

The number of patients enrolled from each medical center and their vital status as of January 1, 1997, is provided in Table 1. Vital status was determined for approximately 89% of patients, and 11% were lost to follow-up. Among the 4971 patients who were located, 985 (20%) were confirmed deceased with death certificate, 61 (1%) were presumed deceased with cause of death unknown, and 3925 (79%) were alive. More than 220,000 woman-years of follow-up were accrued. The average length of follow-up per patient for all enrolled patients was 40.5 years, with center-specific averages ranging from 35 to 45 years. The mean age at follow-up was 51 years (range, 2–89).

Information on personal characteristics and scoliosis history, as derived from medical records, is presented in Table 3. The average year of birth was 1937 (range, 1906–1964) and the average age at diagnosis was 10.1 years (range, 0–19). The earliest year of diagnosis was 1912. The small percentage of cases diagnosed in patients under age 3 reflects that there was no enrollment of congenital scoliosis cases from the 10 medical centers added in the expanded study and the low prevalence of infantile idiopathic scoliosis in the United States. The majority of patients were diagnosed during adolescence (age ≥10 years). Scoliosis was by far the predominant type of deformity (93%), with relatively few patients having lordosis, kyphosis, or kyphoscoliosis.

All patient diagnoses were taken from the medical records. Nearly 50% of patients had idiopathic scoliosis and approximately 25% of patients had neuromuscular

Table 3. Demographic Characteristics, Scoliosis History, and Radiation Exposure Among 5573 Female Patients From 14 U.S. Orthopedic Medical Centers

Characteristic	No. of Patients	Percent
Total	5573	100.0
Year of birth		
<1920	541	9.7
1920–29	1184	21.2
1930–39	923	16.6
1940–49	1908	34.2
≥1950	1017	18.2
Calendar year of scoliosis diagnosis		
<1930	585	10.5
1930–39	1156	20.7
1940–49	870	15.6
1950–59	1452	26.1
≥1960	1510	27.1
Age at scoliosis diagnosis, yr		
≤3 (infantile)	214	3.8
3.1–9.9 (juvenile)	1867	33.5
≥10 (adolescent)	3492	62.7
Type of deformity		
Scoliosis	5167	92.7
Lordosis	209	3.8
Kyphosis	124	2.2
Kyphoscoliosis	73	1.3
Etiology		
Idiopathic	2742	49.2
Neuromuscular, post-polio	1118	20.1
Neuromuscular, other	248	4.5
Congenital*	161	2.9
Postural	492	8.8
Scheuermann's	45	0.8
Traumatic	16	0.3
Neurofibromatosis	15	0.3
Structural, NOS	286	5.1
Other	118	2.1
Unknown	332	6.0
Maximum curve magnitude, degrees		
<30	429	7.7
30–44	644	11.6
45–59	678	12.2
60–74	502	9.0
≥75	468	8.4
Unknown	2852	51.2
Length of time under observation, yr		
<1	1348	24.2
1–4	2258	40.5
5–9	1131	20.3
≥10	836	15.0
Type of treatment		
Surgery	1838	33.0
Cast or brace	276	5.0
Other or unknown	3459	62.1
Number of spinal surgeries		
0	2871	51.5
1	924	16.6
2	538	9.7
≥3	376	6.7
Unknown	864	15.5
Total number of radiographic exams†		
0	631	11.3
1–19	2492	44.7
20–39	1243	22.3
40–59	655	11.8
≥60	552	9.9
Cumulative radiation dose to breast, cGy		
0	688	12.3
<1–9	2627	47.1
10–19	1325	23.8
≥20	932	16.7
Unknown	1	0.0

* Patients with congenital scoliosis were enrolled from the four Minneapolis-St. Paul centers only.
† Includes 11,408 exams for 1847 patients in which the breast was not exposed.

Table 4. Characteristics of Diagnostic Radiographic Exams Received by Scoliosis Patients

Characteristic	Radiographic Exams Number	Radiographic Exams Percent
Total	137,711	100.0
Field		
Full spine	40,652	29.5
Upper and lower spine	21,202	15.4
Cervical spine	271	0.2
Cervicothoracic spine	134	0.1
Thoracic spine	1243	0.9
Thoracolumbar spine	18,451	13.4
Upper spine	9772	7.1
Lumbar spine	655	0.5
Lumbosacral spine	401	0.3
Lower spine	13,588	9.9
Whole body	4013	2.9
Skull	408	0.3
Chest	3766	2.7
Abdomen	332	0.2
Pelvis	2905	2.1
Extremities	3041	2.2
Fluoroscopy	264	0.2
Other	1115	0.8
Unknown	15,498	11.3
View*		
Anteroposterior	88,518	64.3
Posteroanterior	1748	1.3
Lateral	19,351	14.1
Oblique	3746	2.7
Other	252	0.2
Unknown	24,096	17.5

Characteristic	Radiographic Exams Number	Radiographic Exams Percent
Position		
Standing or sitting	41,683	30.3
Supine	20,140	14.6
Bending	6786	4.9
Tilt	1678	1.2
Other	2655	1.9
Unknown	64,769	47.0
Orthosis present		
Yes	13,849	10.1
No or unknown	123,862	89.9
Film size, inches		
14 × 17	57,676	41.9
11 × 14	6390	4.6
10 × 12	3678	2.7
14 × 36	2753	2.0
8 × 10	895	0.6
Other or unknown	66,319	48.2
Breast in the radiation beam*		
Yes	121,161	88.0
Probably	1081	0.8
No	11,408	8.3
Unknown	4061	2.9
Calendar year of exam		
<1940	8101	5.9
1940–59	55,155	40.1
1960–75	70,821	51.4
1976–89	3139	2.3
Unknown	495	0.4

* Distribution is after logical recoding of missing or unknown data using other available information (see Methods).

scoliosis, primarily as an aftermath of poliomyelitis. It should be noted that patients currently diagnosed with idiopathic scoliosis were historically diagnosed due to mild polio infection. Curve measurements were not available from medical records for approximately half the cohort. For the remainder, the largest curve measured while under observation ranged between 3° and 180° (average, 53°). Patients were observed in clinic for 4.8 years on average (range, <1–55 years). There was no indication of any type of treatment for most of the patients. Approximately one-third of the cohort had undergone surgical correction for the curvature, whereas only a small percentage had been treated by cast or brace without surgery. Patients who were treated surgically had a mean of 1.8 surgical procedures (range, 1–8). A total of 137,711 radiographic exposures were tabulated, with the number of examinations per patient ranging from 0 to 618 (average, 24.7). Nearly 15% of patients had undergone 50 or more radiographic examinations and approximately 17% had an estimated cumulative radiation dose to the breast of 20 cGy or greater.

Table 4 presents characteristics of diagnostic radiographic examinations received by patients with scoliosis. Radiographic examinations of the full spine, upper and lower spine, thoracolumbar spine, and lower spine were predominant, and together these represented 68% of all examinations. The anteroposterior view was used predominantly (an estimated 64% of all examinations), whereas posteroanterior views were used infrequently (1%) during the study period. Information on patient positioning was limited, but it appears that most radiographs were taken with patients in the erect position. An orthosis (cast, jacket, brace, or implant) was evident in a relatively small percentage (10%) of examinations. By far, the most commonly used radiograph size was 14 × 17 in. (42%), and most radiographic examinations (89%) involved definite or probable radiation exposure to the breast. There were relatively few examinations before 1940 or after 1975.

Compared with women in the general population, patients with scoliosis had a statistically significant excess risk of dying of all causes (SMR = 1.71; 95% CI = 1.6–1.8), primarily of infectious, circulatory, respiratory, and musculoskeletal conditions. Women with scoliosis had a 1.7-fold risk of dying of breast cancer (SMR = 1.69; 95% CI = 1.3–2.1), and a small nonsignificant excess of deaths were caused by leukemia (SMR = 1.21; 95% CI = 0.6–2.3; 9 cases). There were no excess deaths caused by lung cancer (SMR = 0.73; 95% CI = 0.5–1.1; 29 cases). Average estimated doses to the active bone marrow and lung were low: 1.0 and 4.1 cGy, respectively. Significant dose–response relation-

Table 5. Observed Breast Cancer Deaths Among Scoliosis Patients, Expected Deaths Based on U.S. White Females, and Standardized Mortality Ratios (SMR), According to Scoliosis History

Factor	No. of Patients	Person-Years	No. of Deaths: Observed	Expected	SMR	95% CI	Average No. of Radiographic Exams	Average Dose to Breast (cGy)	Relative Risk*	Homogeneity Test: χ^2, (df), *P*-Value: Unadjusted for Trend in Radiation Dose	Adjusted for Trend in Radiation Dose
Total	5466†	218,976	77	45.62	1.69§	1.3–2.1	23.0	10.9	—	—	—
Calendar year of scoliosis diagnosis											
<1940	1663	79,813	38	27.44	1.38	1.0–1.9	5.9	5.9	1.0	5.47	0.49
1940–59	2299	91,616	34	14.48	2.35§	1.6–3.3	30.2	15.0	1.70	(2)	(1)
≥1960	1504	47,547	5	3.69	1.35	0.4–3.2	30.8	10.3	0.98	0.06	0.48
Age at scoliosis diagnosis, yr											
≤3	211	8902	3	1.18	2.55	0.5–7.5	31.4	15.7	1.0	5.76	5.07
3.1–9.9	1821	79,066	18	16.57	1.09	0.6–1.7	21.9	11.5	0.43	(2)	(1)
≥10	3434	131,007	56	27.88	2.01§	1.5–2.6	23.2	10.2	0.79	0.06	0.02
Etiology											
Idiopathic	2707	100,746	25	16.48	1.52	1.0–2.2	28.5	12.7	1.0	6.29	5.13
Neuromuscular	1341	55,017	26	12.45	2.09§	1.4–3.1	22.5	12.4	1.38	(4)	(3)
Congenital	158	5745	3	0.92	3.25	0.7–9.5	44.3	17.9	2.15	0.18	0.16
Other	937	44,088	15	12.69	1.18	0.7–2.0	8.0	4.5	0.78		
Unknown	323	13,380	8	3.06	2.61§	1.1–5.1	11.2	5.1	1.72		
Maximum curve magnitude, degrees											
<30	428	15,883	5	2.16	2.32	0.8–5.4	19.2	9.1	1.0	2.36	1.68
30–59	1316	48,529	15	6.55	2.29§	1.3–3.8	34.8	15.5	0.99	(3)	(2)
≥60	962	35,305	7	4.57	1.53	0.6–3.2	39.2	17.7	0.66	0.50	0.43
Unknown	2760	119,259	50	32.34	1.55§	1.2–2.0	12.3	6.7	0.67		
Type of treatment‡											
Surgery	1823	71,253	31	12.28	2.52§	1.7–3.6	38.9	18.8	1.0	8.90	1.77
Cast or brace	271	9788	5	1.88	2.66	0.9–6.2	14.5	7.6	1.06	(2)	(1)
Other or not specified	3372	137,936	41	31.46	1.30	0.9–1.8	15.0	7.0	0.52	0.01	0.18
Number of spinal surgeries											
0	2784	117,560	41	29.00	1.41§	1.0–1.9	9.1	4.9	1.0	10.74	3.65
1	915	34,864	12	6.25	1.92	1.0–3.4	33.4	15.8	1.36	(4)	(3)
2	534	21,713	11	3.94	2.79§	1.4–5.0	37.6	19.2	1.97	0.03	0.30
≥3	374	14,676	8	2.09	3.83§	1.7–7.5	54.4	25.4	2.71		
Unknown	859	30,164	5	4.34	1.15	0.4–2.7	34.0	13.8	0.81		

* Relative risks were derived by dividing the SMRs for the higher intervals by the SMR for the lowest interval (referent group) within each stratum.
† Excluded from analysis were 34 patients who contributed no person-years of follow-up, 18 patients for whom exit dates were missing, and 55 patients who were deceased but for whom cause of death was unknown.
‡ Treatment groups are defined as: any surgery; cast or brace without surgery; no evidence of surgery, cast, or brace.
§ $P < 0.05$.
df = degrees of freedom; CI = confidence interval.

ships were observed for deaths from infectious, circulatory, respiratory, digestive, and musculoskeletal conditions (not shown).

The SMRs for breast cancer are presented in Table 5 according to factors related to scoliosis history, and in Table 6 according to factors specifically related to radiation exposure. The excess deaths caused by breast cancer among patients with scoliosis can be seen to vary according to many of these factors.

Risk was highest among patients with disease that was diagnosed during the 1940s and 1950s, although a nearly significant 40% excess SMR was apparent among those with diagnosis before 1940 (Table 5). A significantly increased risk was observed in patients with scoliosis with adolescent (≥10 years) onset; the 2.6-fold risk observed among those with diagnosis in infancy was based on only three cases and was not significant. Patients with neuromuscular and unknown causes had significant 2.1- and 2.6-fold elevated risks, respectively. Significant excesses were apparent in women with maximum spinal curve measurements of 30–59° and in those with unknown measurements. Most of the breast cancers (65%) occurred among women with unknown curve sizes; there were few observed deaths among women with curves of less than 30° or more than 60°. Patients who had undergone surgical correction for their curvature had a significant 2.5-fold greater risk for breast cancer. Patients who were treated with cast or brace without surgery had a similar, although nonsignificant, excess risk based on a small number of cases. There was no increased risk among patients who had no evidence of treatment by surgery, cast, or brace. Risk increased significantly with increasing number of spinal surgeries (P trend = 0.004), with patients who had undergone two and three or more procedures having significant three- and fourfold risks, respectively, of dying of breast cancer.

Risk of breast cancer was evaluated by number of radiographic examinations in which the breasts were exposed, estimated cumulative radiation dose to the breast,

Table 6. Observed Breast Cancer Deaths Among Scoliosis Patients, Expected Deaths Based on U.S. White Females, and Standardized Mortality Ratios (SMR), According to Radiation Exposure

			No. of Deaths							Homogeneity Test: χ^2, (df), *P*-Value	
Factor	No. of Patients	Person-Years	Observed	Expected	SMR	95% CI	Average No. of Radiographic Exams	Average Dose to Breast (cGy)	Relative Risk*	Unadjusted	Adjusted for Trend in Radiation Dose
No. of radiographic exams†‡											
0	644	34,468	7	9.96	0.70	0.3–1.5	0	0	1.0	14.06	2.21
1–24	2845	117,709	47	26.73	1.76¶	1.3–2.3	9.4	5.7	2.50	(3)	(2)
25–49	1269	44,413	12	6.08	1.98¶	1.0–3.5	35.4	16.3	2.81	0.003	0.32
≥50	708	22,387	11	2.85	3.86¶	1.9–6.9	76.2	32.6	5.49		
Cumulative radiation dose to breast, cGy†											
0	643§	34,443	7	9.96	0.70	0.3–1.5	0	0	1.0	14.70	3.83
1–9	2580	104,237	39	22.13	1.76¶	1.3–2.4	9.4	4.4	2.51	(3)	(2)
10–19	1317	47,571	13	8.16	1.59	0.9–2.7	31.7	14.5	2.27	0.002	0.15
≥20	924	32,677	18	5.36	3.36¶	2.0–5.3	64.4	31.9	4.78		
Age at first radiographic exam, yr											
No radiograph	644	31,069	7	9.96	0.70	0.3–1.5	0	0	—		
<10	1458	59,507	14	10.06	1.39	0.8–2.3	31.4	15.9	1.0	9.02	9.02
10–11	938	36,259	23	6.84	3.36¶	2.1–5.1	26.5	13.4	2.42	(3)	(2)
12–13	1491	57,170	21	11.34	1.85¶	1.2–2.8	23.1	10.5	1.33	0.03	0.01
≥14	935	34,971	12	7.42	1.62	0.8–2.8	22.0	8.9	1.16		
Time since first radiograph, yr†											
Unexposed‖	644	34,462	7	9.96	0.70	0.3–1.5	0	0	—		
<20	505	84,587	0	0.93	0.00	0.0–4.0	16.7	10.0	0.0	5.59	4.64
20–29	127	42,586	5	5.10	0.98	0.3–2.3	33.2	15.2	1.0	(3)	(2)
30–39	2038	32,063	25	10.28	2.43¶	1.6–3.6	30.1	11.3	2.48	0.13	0.10
≥40	2152	25,278	40	19.35	2.07¶	1.5–2.8	24.0	13.9	2.11		
Age at study exit, yr†											
<40	783	141,994	2	4.73	0.42	0.1–1.5	19.3	10.2	1.0	5.69	5.13
40–44	453	22,602	10	5.28	1.89	0.9–3.5	38.5	14.9	4.48	(3)	(2)
45–49	1341	17,863	15	6.84	2.19¶	1.2–3.6	30.8	11.6	5.19	0.13	0.08
≥50	2889	36,517	50	28.76	1.74¶	1.3–2.3	17.9	10.2	4.11		

* Relative risks were derived by dividing the SMRs for the higher intervals by the SMR for the lowest nonzero interval (referent group) within each stratum.
† The values presented for number of patients, average number of radiographic exams, and average radiation dose are for patients whose follow-up ended in the designated interval. The value for person-years represents time accrued by all patients during the interval. The number of cancers observed represents cases occurring during the interval, and the number of cancers expected was computed based on person-years accrued during the interval.
‡ Number of radiographic exams in which the breasts were exposed.
§ One woman was excluded who had a single radiographic exam with an unknown dose.
‖ Includes 3393 person-years for 2304 patients who entered the study before their first exposure; 644 patients had no documented radiographic exams.
¶ $P < 0.05$.
df = degrees of freedom; CI = confidence interval.

age at first radiographic examination, time since first radiographic examination, and age at study exit (Table 6). Of the 5466 patients included in the breast cancer analyses, 644 had no exposure (zero dose). Doses were estimated for all but 1 of the remaining 4822 patients. The average estimated cumulative dose to the breast was 10.9 cGy for all 5466 patients and 12.4 cGy for those who were exposed. Risk of breast cancer increased significantly as the number of radiograph exposures increased (*P* trend = 0.0006), and patients who had 50 or more radiographic examinations had a significant, nearly fourfold risk. Similarly, a significant trend in increased risk was observed with cumulative radiation dose (*P* trend = 0.001), and patients who sustained breast doses of 20 cGy or more had a more than threefold significantly greater risk.

Many of the scoliosis history factors are indicators for radiation exposure. For example, patients who had diagnosis at younger ages, were observed for longer periods, or had more severe curves may also have been more frequently radiographed. Further, radiation dose is itself an indicator for severity of disease, which may have an independent influence on breast cancer risk. Mean numbers of radiographic examinations, and the corresponding estimates of cumulative breast tissue dose, are shown in columns 8 and 9 of Tables 5 and 6, indicating the extent to which the levels of various factors are correlated with radiation dose. Column 10 presents the SMR results, rescaled to RR. The degree of nonhomogeneity among the RR values is indicated in column 11 by a χ^2 statistic, with degrees of freedom (*df*) equal to the number of factor levels minus 1, and its *P*. A second χ^2 value in column 12 indicates the amount of nonhomogeneity that cannot be explained as a simple linear trend in radiation dose.

Among scoliosis history factors, there was no evidence of nonhomogeneity of risk by factor level for cause and maximum curve magnitude; there was evidence suggestive of nonhomogeneity ($P < 0.10$) for calendar year and age of scoliosis diagnosis; and there was statistically significant evidence of nonhomogeneity by type of treatment ($P = 0.01$) and number of spinal surgeries ($P =$

Table 7. Observed Breast Cancer Deaths Among Scoliosis Patients, Expected Deaths Based on U.S. White Females, and Standardized Mortality Ratios (SMR), by Age at First Radiographic Exam and Cumulative Radiation Dose to Breast*

Age at First Radiographic Exam, Yr/Dose to Breast, cGy†	No. of Patients	Person-Years	No. of Deaths: Observed	Expected	SMR	95% CI	Average No. of Radiographic Exams	Average Dose to Breast (cGy)	Relative Risk‡
<10 yr									
1–9 cGy	695	31,747	8	6.48	1.23	0.5–2.4	6.5	3.8	1.0
10–19	323	12,190	2	1.68	1.19	0.1–4.3	29.9	15.1	0.96
≥20	440	14,937	4	1.90	2.10	0.6–5.4	71.8	35.5	1.71
10–11									
1–9	409	16,813	13	3.81	3.41§	1.8–5.8	8.2	4.4	1.0
10–19	315	11,049	3	1.80	1.67	0.3–4.9	30.6	14.8	0.49
≥20	214	7671	7	1.23	5.69§	2.3–11.7	55.3	28.9	1.67
12–13									
1–9	831	32,072	12	6.85	1.75	0.9–3.1	10.8	4.8	1.0
10–19	484	17,292	4	3.12	1.28	0.3–3.3	32.1	13.9	0.73
≥20	176	6603	5	1.37	3.65	1.2–8.5	55.9	28.2	2.08
≥14									
1–9	645	23,605	6	4.99	1.20	0.4–2.6	11.5	4.4	1.0
10–19	195	7040	4	1.56	2.57	0.7–6.6	35.7	14.3	2.13
≥20	94	3466	2	0.86	2.34	0.3–8.4	66.1	29.0	1.93

* Excluding 644 patients with no exposure.
† The values presented for number of patients, average number of radiographic exams, and average radiation dose are for patients whose follow-up ended in the designated interval. The value for person-years represents time accrued by all patients during the interval. The number of cancers observed represents cases occurring during the interval, and the number of cancers expected was computed based on person-years accrued during the interval.
‡ Dose-specific relative risks by age were derived by dividing the SMRs for the higher dose intervals by the SMR for the lowest dose interval (referent group) within each age stratum.
§ $P < 0.05$.
CI = confidence interval.

0.03; Table 5). There was no significant nonhomogeneity by treatment center (data not shown). Most of the variation by year of diagnosis, type of treatment, and number of surgeries could be explained by differences in average radiation dose; however, correction for dose did not explain the variation by age at scoliosis diagnosis ($P = 0.02$).

Risk differed significantly by level of cumulative radiation dose, number of radiographic examinations, and age at first radiographic examination, but not by time since first radiographic examination or age at study exit (Table 6). The variation by cumulative dose (nonhomogeneity χ^2 14.70 with 3 *df*) could be explained by a significant linear trend in average dose (χ^2 10.87 with 1 *df*), leaving no significant residual (χ^2 3.83 with 2 *df*). The same linear pattern was observed for number of radiographic examinations. For patients with radiograph exposure, there was significant variation in risk by age at first radiographic examination ($P = 0.03$), even after adjustment for dose ($P = 0.01$).

The significant residual nonhomogeneity of risk among the four intervals of age at first radiographic examination (<10, 10–11, 12–13, and ≥14 years) reflects a 3.4-fold SMR among patients first exposed at ages 10 or 11 *versus* 1.4–1.9-fold for younger and older exposure ages. This difference at first suggested the possibility of differential sensitivity to radiation carcinogenesis; however, separate dose–response analyses by age at first radiographic examination found high SMR values in the 10–11 year age group at low and high dose levels (Table 7). Thus, using the 1–9 cGy interval as the referent for each age group, there was very little difference by age group in dose-specific relative risks (Table 7, right-most column).

Poisson model, linear dose–response analyses were performed, with and without adjustment for other factors (Table 8). The estimated ERR at 1 Gy was 5.4 (95% CI = 1.2–14.1) with no adjustment factor. Adjustment for age at diagnosis of scoliosis improved the fit somewhat ($P = 0.09$) but had little effect on the dose–response coefficient, whereas adjustment for cause, year of diagnosis, surgery, and degree of curvature did not improve fit and had little effect on the estimate. However, adjustment for type of treatment ($P = 0.23$) and age at first radiographic examination ($P = 0.02$) each reduced the dose–response coefficient by approximately half.

The 644 women with no recorded radiographic examinations may not be representative of the remainder of the study population. For example, 76% had disease diagnosed before 1940 (compared with 24% of the women with at least one recorded radiographic examination), 53% (compared with 31%) had juvenile onset, 13% (compared with 54%) had disease of idiopathic origin, 63% (compared with 18%) were seen in clinic for less than 1 year, 98% (compared with 44%) had unknown maximum curvature, and 4% (compared with 55%) had undergone corrective surgery. Poisson regression analyses restricted to patients who had received at least one radiographic examination revealed an estimated ERR of 2.7/Gy (95% CI = −0.2–9.3; Table 8).

Table 8. Summary of Poisson Model, Linear Dose-Response Analyses, With and Without Adjustment for Other Variables

	All Patients		Patients With ≥1 Radiographic Exam	
Adjusted For	ERR at 1 Gy (95% CI)	*P*-Value for Adjustment	ERR at 1 Gy (95% CI)	*P*-Value for Adjustment
None	5.4 (1.2–14.1)	—	2.7 (−0.2–9.3)	—
Etiology	6.4 (1.3–19.1)	.22	3.2 (−0.1–11.8)	.33
Age at diagnosis	4.8 (0.9–12.7)	.09	2.7 (−0.2–9.3)	.27
Year of diagnosis	4.0 (0.3–12.3)	.46	2.1 (−0.6–8.5)	.57
Surgery	4.7 (−0.3–21.5)	.44	1.8 (<0–10.8)	.36
Treatment	3.2 (−0.3–11.7)	.23	1.5 (−0.9–7.6)	.21
Curvature	7.0 (1.3–20.8)	.61	3.6 (−0.1–13.2)	.67
Age at first radiograph	2.5 (−0.3–8.9)	.02	2.5 (−0.3–8.9)	.05

ERR = excess relative risk; CI = confidence interval.

With this constraint, similar estimates were obtained after adjustment for the other factors, but no improvement in fit was observed except after adjustment for age at first radiographic examination ($P = 0.05$).

A formal Poisson analysis of nonhomogeneity of dose–response by age at first radiographic examination yielded $P = 0.82$ (not shown). In general, a patient received radiographic exposure over a period of years. Analyses of dose response by age at exposure (<10, 10–11, 12–13, and 14 years of more; also not shown) yielded statistically unstable age-specific dose–response coefficients, with no persuasive evidence of nonhomogeneity of risk by age at exposure. The χ^2 tests for nonhomogeneity produced $P = 0.13$ for an unadjusted analysis and $P = 0.42$ for an analysis adjusted for age at first exposure.

■ Discussion

Mortality among patients with scoliosis has been evaluated in several studies.[1,5,10,11,25–27,31,36] In general, cardiac and respiratory diseases accounted for most of the deaths; few cancer deaths were observed. Similar to previous studies,[26,27] the overall risk of mortality among the 5573 patients in the current study was approximately two times greater than among women in the general population. Previously, a 1.8-fold risk for incident breast cancer was reported by the authors among the 1030 patients from the four Minneapolis–St. Paul medical centers.[13] The current finding of a 69% excess in breast cancer mortality was essentially unchanged (SMR = 1.65) when pilot study patients were excluded.

Consistent with radiation as a causative factor, risk of dying of breast cancer increased significantly with number of radiographic examinations in which the breast was exposed and with increasing cumulative radiation dose to the breast. The observed ERR at 1 Gy of 5.4 is higher than has been obtained in studies of breast cancer mortality in other populations exposed to radiation at similar ages,[14,17,31] although the confidence limits are wide and statistically consistent with other estimates. As previously mentioned, it is possible that patients for whom no radiographic examinations were recorded may be an unsatisfactory comparison group. When analyses were restricted to patients who received at least one radiographic examination, the estimated ERR was halved (to 2.7/Gy).

The finding of nonhomogeneity of the SMR by age at first radiographic examination, with a significant 3.4-fold risk among patients first examined at 10–11 years of age compared with a consistent 40–85% excesses for younger and older age groups, was intriguing in view of Korenman's[15] "window hypothesis" that breast tissue may be more susceptible to carcinogenic injury during early breast budding, before the onset of menarche. However, the excess did not reflect a stronger association of risk with radiation exposure at a particular age (*e.g.*, 10–11 years of age). The SMR estimates were nearly uniformly higher among women first radiographed at age 10–11, regardless of cumulative dose. The finding remains unexplained.

Similar to the studies of patients in Massachusetts with tuberculosis[3] and atomic bomb survivors,[34] risk of breast cancer increased with time since exposure up to 40 years, and remained high thereafter. Consistent with results in the tuberculosis studies,[20] analyses by attained age did not indicate a radiation-related excess risk of early-onset breast cancer similar to that observed among atomic bomb survivors.[34]

Although radiation dose was positively and strongly related to breast cancer risk in these data, it did not explain all the variation in risk, whether expressed in terms of SMR or relative risk, for some factors covered in Tables 5 and 6. As discussed, there was significantly more variation in relative risk among categories of age at first radiographic examination than could be explained by a linear correlation to radiation dose, and dose response did not differ by age at first radiographic examination. A similar difference, also not explained by differences in dose or dose response, was observed for age at scoliosis diagnosis, and this also remains unexplained. Nearly all the observed nonhomogeneity corresponded to a higher breast cancer risk among women exposed at age 10 or older.

Several methodologic strengths and limitations should be considered when interpreting the findings from the current investigation. This is by far the largest cohort of patients with scoliosis accumulated to date, and follow-up is complete for 89% of patients. More than 220,000 woman-years of follow-up were accrued, with a per patient average period of observation of more than 40 years. The number of radiographic examinations received by each patient at the participating medical centers was accurately tabulated through detailed review of medical records and radiographs, and breast doses were estimated using actual machine parameters derived from one medical center for which information was available during most of the calendar periods covered.

The nonspecific elevation in SMR for nearly all major causes of death prompted concern about whether ascertainment of deaths in this population was more complete than location of living patients. If so, discontinuing follow-up for patients who were lost at dates last known alive could have led to an overestimation of the SMRs. However, when it was assumed that patients who were lost to follow-up remained alive until the end of study (January 1, 1997), the SMRs were essentially unchanged for all causes of death (1.69 compared with 1.71) and for breast cancer (1.67 compared with 1.69), and significant excess risks and dose–response relationships persisted for the major causes of death.

The estimated cumulative radiation dose to the breast may be subject to substantial downward bias, as well as random error, for several reasons. First, although hospitals were selected based on the completeness of their available records during all periods covered, some examinations may have been missed due to lost or destroyed radiographs or medical records. Second, there was limited or no information on radiographic examinations before referral to the participating center or after the last visit. Before 1965, it is unlikely that patients were observed by a general practitioner; more likely, they were referred to an orthopedic treatment center. Also, unless there are late complications, patients are typically monitored only until the growth spurt is completed. Third, information was not available on examinations that were repeated, owing to poor image quality. In general, second radiographs are not recorded; however, radiology technologists at the participating centers estimated retake rates of 2–5%. It would be expected that the number of retakes for spinal examinations would be relatively small because the primary goal of the examination is to image the shape of the spine rather than to examine fine structure. Fourth, there was much uncertainty about the doses delivered in the early years and for certain procedures, such as fluoroscopy. Doses for examinations before 1940 were considered to be twice those for examinations in 1940 or later, on average. Although the earlier doses could have been considerably higher, the number of affected examinations was relatively small (<6% of all examinations). Doses for fluoroscopic examinations in all calendar periods were considered to be twice that of full spine examinations in the same periods and, again, these doses could have been much higher. There were very few fluoroscopic examinations, however (n = 264). When doses from fluoroscopic and nonfluoroscopic examinations were separated in the analysis, there was no improvement in fit ($P = 0.96$), and the risk coefficient for nonfluoroscopic dose did not differ from that for total dose. None of the potential sources of error just mentioned seem likely to have created a spurious association between radiation dose and breast cancer deaths, but the overall effect could be to underestimate cumulative dose and overestimate the risk coefficient.

Additionally, it is unclear whether the general population is an appropriate comparison group for women with scoliosis. Dose appears to be highly correlated with severity of scoliosis, which may be independently related to dying of infectious, circulatory, respiratory, digestive, and musculoskeletal conditions. This will be evaluated further in a subsequent study. It is possible that some of the excess observed breast cancers were due to differences between the two populations in other breast cancer risk factors, such as reproductive history, which may also be linked to both severity of disease and cumulative dose. Reproductive information on individual women who died of breast cancer were not available, and there was no adjustment for these factors. Data from more than 3100 patients who completed a questionnaire during 1993 and 1994 indicate that nulliparity was more common among those with larger curves (32%, 27%, and 24%, respectively, among patients with ≥60°, 30–60°, and <30° curves) and patients who had undergone surgical procedures (31%) compared with those who had not (24%)—factors that are also related to greater radiographic exposure (see Table 5). Thus, the observed increased risk may be confounded by reproductive history and/or severity of disease. It is significant in this respect that deleting patients with no record of radiographic examination, who may well have had less severe scoliosis, yielded a dose–response coefficient of 2.7 for ERR at 1 Gy.

Ionizing radiation exposure is a very well established breast cancer risk factor, especially when exposure occurs during childhood or adolescence.[18] Thus, it is likely that the high level of dose-related risk observed reflects both the dose–response correlation for the general population and some degree of correlation between exposure and other breast cancer risk factors, mediated by severity of disease.

Most of the examinations in this study were made before 1976, when the dose to patients was considerably higher than with current techniques. For example, the adult (≥13 years) breast dose from a full-spine anteroposterior view in 1940–1959 was approximately six times higher than the dose in 1976–1989, as shown in Table 2. Furthermore, using posteroanterior rather than anteroposterior views reduces the breast doses significantly. With more recent techniques, a full spine posteroanterior view provides a breast dose approximately 20 times lower than the anteroposterior view. Although low, there is still a projected excess risk for breast cancer using modern radiography techniques,[19] and it is recommended that every effort be made to reduce exposures further by using the posteroanterior view, proper collimation, and shielding, as well as minimizing repeat exposures resulting from poor image quality.[9]

Key Points

- A retrospective cohort study was conducted in 5573 female patients with scoliosis who were treated at any of 14 orthopedic treatment centers in the United States from 1912 through 1965.
- Patients underwent an average of 25 radiographs, and the mean estimated radiation dose to the breast was 10.8 cGy.
- A statistically significant 70% excess risk of dying of breast cancer was observed compared with the general population.
- Patterns were consistent with radiation as a causative factor, in that risk increased with increasing number of diagnostic radiographic examinations and cumulative radiation dose to the breast.
- Potential confounding between radiation dose and severity of disease may explain some of the excess risk observed.

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